VOLUME 33 · NUMBER 1 · JANUARY 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance)

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See accompanying editorial on page 1

A B S T R A C T

Purpose

One third of patients with triple-negative breast cancer (TNBC) achieve pathologic complete response (pCR) with standard neoadjuvant chemotherapy (NACT). CALGB 40603 (Alliance), a 2 × 2 factorial, open-label, randomized phase II trial, evaluated the impact of adding carboplatin and/or bevacizumab.

Patients and Methods

Patients (N = 443) with stage II to III TNBC received paclitaxel 80 mg/m^2 once per week (wP) for 12 weeks, followed by doxorubicin plus cyclophosphamide once every 2 weeks (ddAC) for four cycles, and were randomly assigned to concurrent carboplatin (area under curve 6) once every 3 weeks for four cycles and/or bevacizumab 10 mg/kg once every 2 weeks for nine cycles. Effects of adding these agents on pCR breast (ypT0/is), pCR breast/axilla (ypT0/isN0), treatment delivery, and toxicities were analyzed.

Results

Patients assigned to either carboplatin or bevacizumab were less likely to complete wP and ddAC without skipped doses, dose modification, or early discontinuation resulting from toxicity. Grade ≥ 3 neutropenia and thrombocytopenia were more common with carboplatin, as were hypertension, infection, thromboembolic events, bleeding, and postoperative complications with bevacizumab. Employing one-sided *P* values, addition of either carboplatin (60% *v* 44%; *P* = .0018) or bevacizumab (59% *v* 48%; *P* = .0089) significantly increased pCR breast, whereas only carboplatin (54% *v* 41%; *P* = .0029) significantly raised pCR breast/axilla. More-than-additive interactions between the two agents could not be demonstrated.

Conclusion

In stage II to III TNBC, addition of either carboplatin or bevacizumab to NACT increased pCR rates, but whether this will improve relapse-free or overall survival is unknown. Given results from recently reported adjuvant trials, further investigation of bevacizumab in this setting is unlikely, but the role of carboplatin could be evaluated in definitive studies, ideally limited to biologically defined patient subsets most likely to benefit from this agent.

J Clin Oncol 33:13-21. © 2014 by American Society of Clinical Oncology

INTRODUCTION

Triple-negative breast cancer (TNBC), characterized by absent or minimal expression of estrogen (ER) and progesterone receptors (PgRs) and human epidermal growth factor receptor 2 (HER2), accounts for 15% to 20% of invasive breast cancers diagnosed in the United States. It is more common in younger women, African Americans, Hispanics, and *BRCA1*-mutation carriers. With no targetable characteristic molecular abnormalities yet identified, standard treatment for TNBC remains chemotherapy. In early-stage TNBC, recurrence-free (RFS) and overall survival (OS) are improved significantly with adjuvant chemotherapy, including dose-dense treatment,[1] but overall prognosis remains inferior to that of other breast cancer subtypes, with higher risk of early relapse, often involving viscera or the CNS.

Approximately one third of patients with stage II to III TNBC treated with anthracycline- and taxane-based neoadjuvant chemotherapy (NACT) achieve a pathologic complete response (pCR). As in

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Published online ahead of print at www.jco.org on August 4, 2014.

Processed as a Rapid Communication manuscript.

Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT00861705.

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0732-183X/15/3301w-13w/$20.00

DOI: 10.1200/JCO.2014.57.0572

other aggressive cancers, pCR is associated with improved outcomes, whereas patients with residual disease have an increased risk of recurrence.[2,3]

Platinum analogs attack cancer cells by inducing double-stranded DNA breaks. As single agents, they have limited efficacy in heavily pretreated metastatic breast cancer,[4] but greater activity has been seen in *BRCA*-mutation carriers, with pCR rates > 70% in small neoadjuvant trials.[5,6] *BRCA*-mutated and sporadic TNBC have similar biologic characteristics and mRNA gene expression patterns, motivating further study of platinums in this subtype.[7] Although single-agent cisplatin yielded few pCRs in sporadic TNBC,[8] pilot studies of the addition of cisplatin or carboplatin to standard NACT have reported rates as high as 75%.[9,10]

Bevacizumab binds and inactivates vascular endothelial growth factor 1, believed to support the growth and maintenance of tumor neovasculature necessary for survival and metastasis. In metastatic TNBC, addition of bevacizumab to once-per-week paclitaxel improves response rates and time to progression.[11,12] Whether the addition of bevacizumab to NACT in TNBC could improve pCR rates and long-term outcomes was unknown.

The CALGB (Cancer and Leukemia Group B) 40603 trial was designed to examine the impact of adding carboplatin and/or bevacizumab to conventional NACT in TNBC on clinical activity, measured by pCR rates, and toxicity. Correlative studies to identify markers of response and resistance, including intrinsic subtype (basal-like *v* others), will be reported separately.

PATIENTS AND METHODS

Patient Population

Eligible patients had operable, biopsy-confirmed, previously untreated, clinical stage II to III noninflammatory invasive breast cancer, with ER and PgR expression ≤ 10% and HER2 negativity, defined by immunohistochemical (IHC) staining 0 to 1+ or fluorescence in situ hybridization ratio < 2.0 if IHC 2+ or IHC not performed. Adequate hematologic, renal, and hepatic function, normal cardiac function by echocardiogram or radionuclide ventriculogram, and a negative pregnancy test in women of childbearing potential were required. Patients were excluded for grade ≥ 2 neuropathy or contraindications to treatment with bevacizumab, including uncontrolled hypertension.

Study Procedures

Magnetic resonance imaging was preferred for baseline breast imaging. In patients with clinical stage III disease, imaging studies to rule out overt metastatic disease were recommended. Surgeons were asked to assess patient eligibility for breast-conserving surgery (BCS) before treatment. In patients with clinically positive axillae, histologic confirmation by biopsy or fine-needle aspiration was encouraged. Patients with clinically negative axillae could undergo pretreatment sentinel lymph node (SLN) sampling. Tumor biopsies for correlative studies—two fixed cores in RNAlater and formalin and, where feasible, two frozen cores in optimal cutting temperature compound—were required.

Figure 1 illustrates the treatment schema. All patients received paclitaxel 80 mg/m^2 once per week (wP) for 12 weeks followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 once every 2 weeks with myeloid growth factor support (ddAC) for four cycles. They were randomly assigned to receive wP with or without concurrent carboplatin at an area-under-the curve (AUC) dose of 6 once every 3 weeks for four cycles and independently to treatment with or without bevacizumab 10 mg/kg once every 2 weeks for nine cycles during administration of wP and the first three cycles of ddAC. Patients were examined every 2 to 3 weeks; patients experiencing progression during wP administration were switched to ddAC, whereas progression while receiving ddAC resulted in early surgery.

wP was skipped for an absolute neutrophil count (ANC) < 800/μL or platelet count < 50,000/μL and permanently reduced by 10 mg/m^2 if treatment was held 2 consecutive weeks for neutropenia, if ANC was < 100/μL at any time, or if febrile neutropenia or grade 2 peripheral neuropathy occurred. Carboplatin was delayed for platelet count < 75,000/μL and permanently reduced by 25% after a 2-week delay for thrombocytopenia or platelet count < 25,000/μL at any time. Bevacizumab dose was never reduced, but treatment was held for ANC < 500/μL, platelet count < 50,000/μL, uncontrolled hypertension, or any grade 3 toxicity attributed to this agent. ddAC was delayed for ANC < 1,000/μL or platelet count < 75,000/μL, and both agents were dose reduced for treatment delay > 1 week or febrile neutropenia.

After completing NACT, patients underwent repeat cardiac evaluation and reassessment of eligibility for BCS, followed by surgery, 4 to 8 weeks after cycle four of ddAC, thus at least 6 weeks after the last dose of bevacizumab. Axillary sampling was required except in patients with negative SLNs pretreatment, but extent of surgery and subsequent irradiation were determined by the treating physicians. Core biopsies of residual tumor were obtained in consenting patients. Patients were monitored for immediate and delayed postsurgical

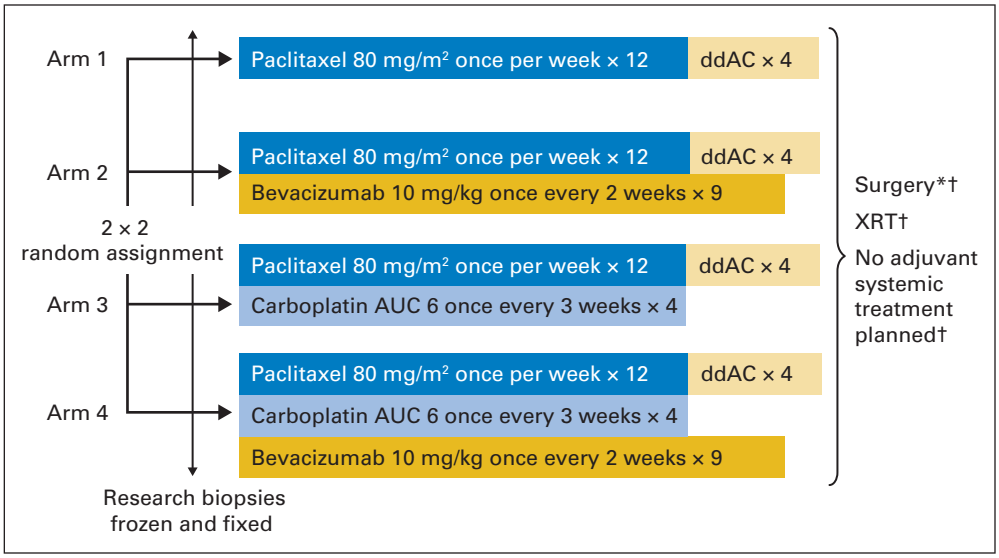

Fig 1. Schema of randomized phase II CALGB (Cancer and Leukemia Group B) 40603 trial. ddAC, dose-dense doxorubicin plus cyclophosphamide. (*) Research biopsies if residual tumor. (†) Physician discretion.

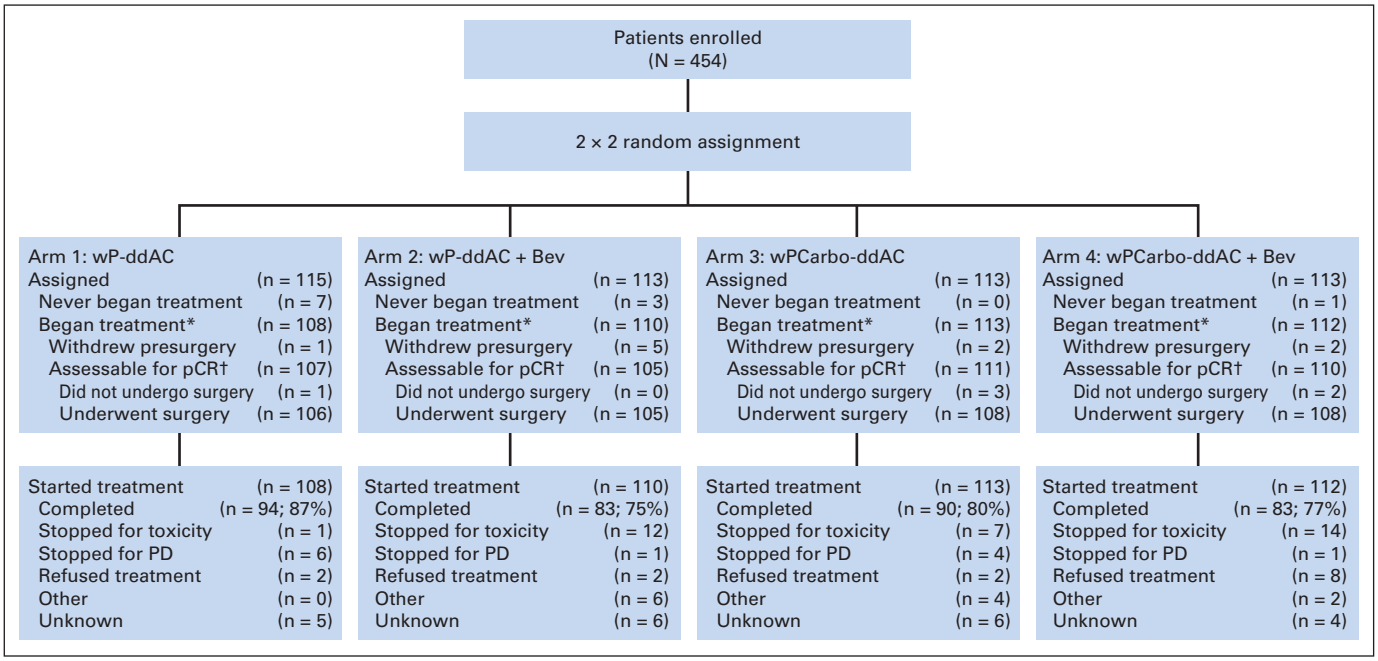

Fig 2. CONSORT diagram. Bev, bevacizumab; Carbo, carboplatin; ddAC, dose-dense doxorubicin plus cyclophosphamide; pCR, pathologic complete response; PD, progressive disease; wP, paclitaxel once per week.

complications. No postoperative adjuvant therapy was planned, but additional systemic therapy was not prohibited.

Pathologic Evaluation

Pathologic response was determined locally, without central pathologic review. pCR breast was defined as the absence of residual invasive disease with or without ductal carcinoma in situ (ypT0/is). pCR breast/axilla was defined as pCR breast and the absence of any tumor deposit $\geq$ 0.2 mm in sampled axillary nodes (ypT0/isN0). Patients with pCR breast and negative pretreatment SLNs were considered to have achieved pCR breast/axilla. For non-pCRs, pathologists were asked to record residual cancer burden (RCB).[13]

Data Collection and Analysis

CALGB 40603 was a randomized, open-label phase II study. After stratification by baseline clinical stage (II *v* III), patients had an equal probability of assignment to any of the four treatment arms. A modified intent-to-treat approach that included all patients who began treatment was used for analyses. Patients who withdrew consent for subsequent data submission before completing NACT were excluded from pCR analyses, whereas those who remained in the study but did not undergo surgery were considered to be non- pCRs.

The study used a 2 × 2 factorial design. Statistical power was based on two separate and independent pairwise comparisons—one for each factor (carboplatin and bevacizumab)—of pCR breast between the control and experimental groups using a 1-*df* χ^2 test. 95% CIs around pCR rates were calculated using binomial methods. To evaluate interactions between factors and clinical stage, corresponding terms were included in logistic regression models; however, because the study was not powered to test interactions, resulting *P* values were considered descriptive and not formal assessments of significance.

The overall study was designed to detect increases in the pCR breast rate from 35% in the control group to 55% for either carboplatin or bevacizumab (one-sided α of 0.05). To test these hypotheses in the subpopulation of basal-like tumors (defined by gene expression analysis) with 90% power, 210 such patients were required. To achieve this goal, study accrual was increased to 445 patients, resulting in > 95% power in the overall study population. All analyses were conducted by CALGB (Alliance) statisticians using SAS software (version 9.2; Cary, NC).

Secondary end points included pCR breast/axilla, treatment delivery, treatment-related toxicities (as defined by Common Toxicity Criteria for Adverse Events, version 4.0), RCB, conversion from clinically node-positive to pathologically node-negative status, and conversion from BCS-ineligible to BCS-eligible status after treatment. Patients will be monitored for RFS, time to first failure, and OS for 10 years.

Study data were collected and data quality monitored by the CALGB (Alliance) Statistics and Data Center and the study chair according to group policies and stored in the CALGB (Alliance) database. The cutoff for this report was October 2013.

The protocol was approved by the central institutional review board of the National Cancer Institute and institutional review boards at participating sites. All patients provided written informed consent. The National Cancer Institute Cancer Therapy Evaluation Program, Genentech USA, a division of F. Hoffman-La Roche, and the Breast Cancer Research Foundation provided support for this trial and were permitted to review the manuscript before submission. Additional funding from the American Recovery and Reinvestment Act to the Coalition for Cancer Cooperative Groups supported implementation of an integrated accrual plan.

RESULTS

Patient Characteristics

Between May 2009 and August 2012, 454 patients were enrolled; 11 never started protocol treatment (CONSORT diagram shown in Fig 2). Characteristics of the 443 treated patients are listed in Table 1. Most were between ages 40 and 59 years; 72% were white, including 8% Hispanic, and 20% were black. Two thirds had clinical stage II disease. The majority had T2 tumors; slightly > half were clinically node positive; 76% had high-grade disease; > 90% had invasive ductal carcinomas, whereas few had ER (6%) or PgR (4%) expression > 1% (data not shown). Baseline characteristics were generally well balanced among treatment arms, but a higher percentage of patients judged

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Total Patients (N = 443) No.	%	Arm One: wP → ddAC (n = 108; %)	Arm Two: wP → ddAC + Bev (n = 110; %)	Arm Three: wPCarbo → ddAC (n = 113; %)	Arm Four: wPCarbo → ddAC + Bev (n = 112; %)
Age, years						
< 40	103	23	21	28	20	23
40-59	266	60	59	57	57	67
≥ 60	74	17	19	15	23	10
Race						
White	320	72	73	74	71	71
Black	89	20	19	19	24	19
Asian	13	3	1	5	4	3
Other/missing	21	5	7	2	1	7
Clinical stage						
II	300	68	69	66	68	67
III	143	32	31	34	32	33
Tumor grade						
Low	6	1	0	2	2	2
Intermediate	47	11	8	13	10	12
High	336	76	83	72	75	73
Missing	54	12	8	14	13	13
T stage						
1	48	11	6	14	11	13
2	288	66	72	60	63	65
3	88	20	19	25	19	17
4	10	2	2	0	4	4
Missing	9	2	2	1	4	1
N stage						
0	186	42	45	38	42	42
1	184	42	42	47	41	37
2	34	8	6	7	7	10
3	9	2	3	1	1	4
Missing	30	7	4	6	9	8

BCS Candidate*	(n = 414)		(n = 101)		(n = 103)		(n = 104)		(n = 106)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Yes	236	57	62	61	67	65	57	55	50	47
No	178	43	39	39	36	35	47	45	56	53

Abbreviations: BCS, breast-conserving surgery; Bev, bevacizumab; Carbo, carboplatin; ddAC, dose-dense doxorubicin plus cyclophosphamide; wP, paclitaxel once per week.
*On basis of surgeon's baseline assessment.

BCS ineligible at baseline were assigned to arms three and four. Of 52 clinically node-negative patients who underwent pretreatment SLN sampling, 14 had at least one positive node.

Clinical Efficacy

The impact of the addition of carboplatin and/or bevacizumab on the primary end point (pCR breast) is illustrated in Figure 3A. Adding either agent significantly increased the pCR breast rate; 60% of patients who received carboplatin achieved pCR breast compared with 46% of those who did not (odds ratio [OR], 1.76; $P = .0018$). Patients treated with a bevacizumab-containing regimen had a pCR breast rate of 59% compared with 48% of those who were not (OR, 1.58; $P = .0089$). Patients assigned to both agents (arm four) had the highest pCR breast rate (67%), with no significant interaction between their effects ($P = .52$).

Secondary End Points

pCR breast/axilla rates were also higher with the addition of carboplatin or bevacizumab (Fig 3B). With carboplatin, the percentage of patients who achieved pCR breast/axilla increased significantly from 41% to 54% (OR, 1.71; $P = .0029$), whereas the increase in the pCR breast/axilla rate with bevacizumab (52% *v* 44%) did not achieve statistical significance (OR, 1.36; $P = .057$). Again, patients who received both agents had the highest pCR rate (60%), with no significant interaction between their effects ($P = .43$).

pCR rates were higher with carboplatin or bevacizumab in both clinical stage II and III disease. Exploratory analyses did not demonstrate a differential effect on pCR for either agent by clinical stage. Other measures of response, including percentage of patients with either pCR breast/axilla or minimal residual disease (RCB classes 0 and I) and conversion from clinically node-positive to pathologically

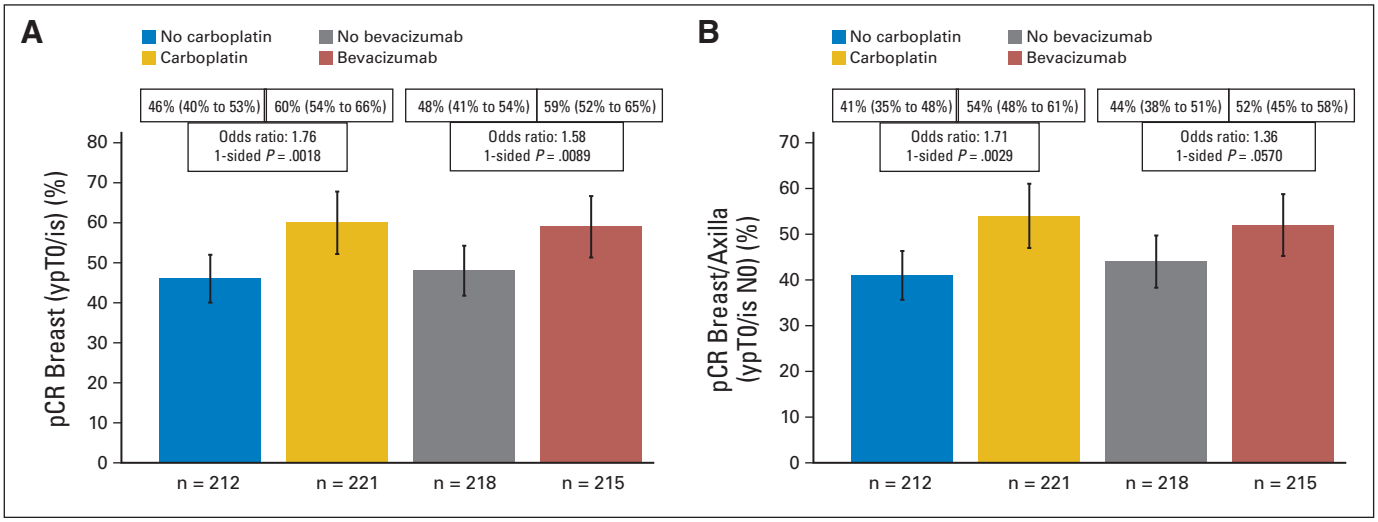

Fig 3. (A) Pathologic complete response (pCR) breast (ypT0/is); (B) pCR breast/axilla (ypT0/is N0); 95% CIs shown in parentheses.

node-negative status, generally followed the same pattern (Table 2). Of patients judged ineligible for BCS at baseline, more were considered BCS eligible after treatment with either carboplatin (57% *v* 44%) or bevacizumab (54% *v* 49%), although these differences were not statistically significant. The percentage of patients who actually underwent BCS, by treatment arm, and other surgical end points will be reported at a later date.

Treatment Delivery and Toxicity

Figure 4 illustrates delivery of wP and ddAC by treatment arm. Patients assigned to carboplatin were more likely to miss ≥ two doses of wP (36% *v* 16%), but only those assigned to both carboplatin and bevacizumab (arm four) were substantially more likely to miss ddAC. Patients assigned to either investigational agent were more likely to require dose reduction of wP (26% *v* 12%) or ddAC (22% *v* 8%) compared with controls (data not shown). Because of treatment delays and toxicities, only 80% of patients assigned to carboplatin received all four planned doses, and only 66% of patients assigned to bevacizumab received ≥ eight of nine planned doses. Patients receiving the control regimen (arm one) were more likely to complete NACT per protocol (87%); only one patient (< 1%) discontinued treatment because of toxicity, and six (6%) did so because of progressive disease (Fig 2). Patients assigned to the experimental arms were more likely to stop treatment early because of toxicity, including seven

Table 2. Response Data

End Point	No Carbo: Arms One and Two (n = 212; %)	With Carbo: Arms Three and Four (n = 221; %)	No Bev: Arms One and Three (n = 218; %)	With Bev: Arms Two and Four (n = 215; %)	Arm One: Control (n = 107; %)	Arm Two: With Bev (n = 105; %)	Arm Three: With Carbo (n = 111; %)	Arm Four: With Bev and Carbo (n = 110; %)
Primary								
pCR breast	46	60	48	59	42	50	53	67
95% CI, %	40 to 53	54 to 66	41 to 54	52 to 65				
OR	1.76		1.58					
P	.0018*		.0089*					
Clinical stage II	45	60	47	59	42	49	51	70
Clinical stage III	48	60	50	59	42	55	57	62
Secondary								
pCR breast/axilla	41	54	44	52	39	43	49	60
95% CI, %	35 to 48	48 to 61	38 to 51	45 to 58				
OR	1.71		1.36					
P	.0029*		.0570*					
Clinical stage II	41	55	44	52	41	42	47	63
Clinical stage III	41	53	44	50	36	45	51	54
Clinical N+ → pN0	65	75	69	71	67	62	70	80
RCB 0 + I	56	67	55	68	51	61	59	75
BCS ineligible → eligible	44	57	49	54	41	47	55	59
95% CI, %	33 to 55	48 to 66	39 to 59	44 to 64				

Abbreviations: BCS, breast-conserving surgery; Bev, bevacizumab; Carbo, carboplatin; OR, odds ratio; pCR, pathologic complete response; RCB, residual cancer burden.
*One sided.

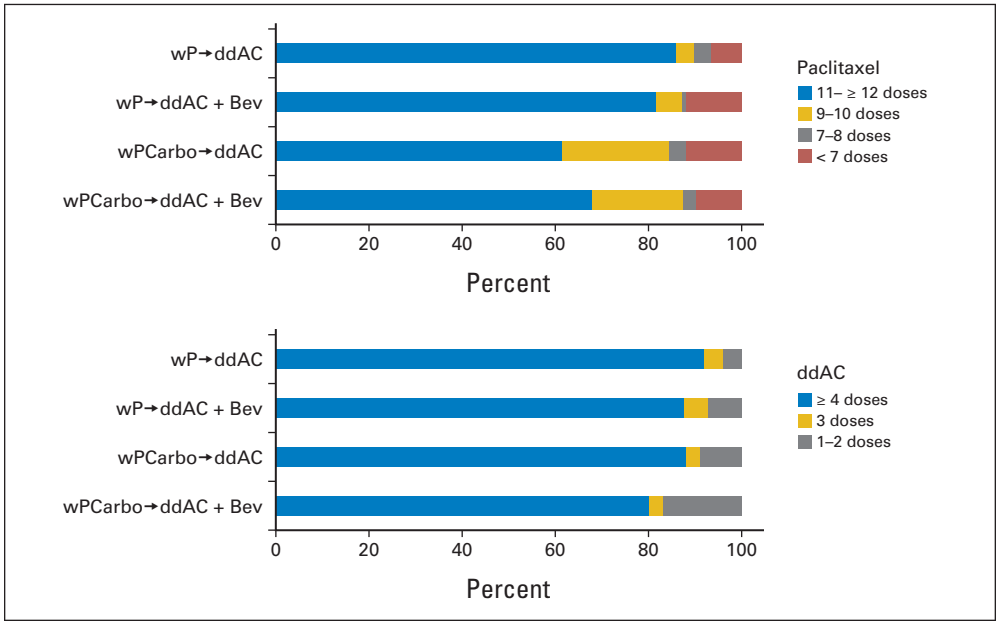

Fig 4. Once-per-week paclitaxel (wP) and dose-dense doxorubicin plus cyclophosphamide (ddAC) treatment by delivery arm. Bev, bevacizumab; Carbo, carboplatin.

(6%) for carboplatin only and 26 (12%) for bevacizumab with or without carboplatin, refusal of further treatment, or unspecified reasons. Four patients (3%) assigned to carboplatin only and two (< 1%) assigned to bevacizumab (arms two and four) stopped treatment early because of disease progression.

Table 3 lists grade ≥ 3 toxicities. Incidence of grade 3 to 4 neutropenia and thrombocytopenia was higher with the addition of carboplatin; however, incidence of febrile neutropenia, which usually occurred during treatment with ddAC, was significantly higher only in arm four. Compared with the non–bevacizumab-containing regimens, patients assigned to bevacizumab were more likely to develop grade 3 hypertension (10% to 12% *v* 0% to 2%), and the only on-study death was attributed to uncontrolled hypertension. The overall number of serious adverse events (Appendix Table A1, online only), defined as any unexpected grade ≥ 3 toxicity or toxicity requiring hospitalization or surgical intervention, was higher with the investigational agents, especially bevacizumab; they included febrile neutropenia, infection without neutropenia, nausea/vomiting, diarrhea and dehydration, bleeding complications, thromboembolic events, and GI perforations. Incidence of immediate (9% *v* 5%) and delayed (4% *v* 1%) postoperative complications requiring intervention was also higher with the addition of bevacizumab.

Table 3. Grade 3 to 4 Treatment-Related Toxicities

	Arm One: Control (%)	Arm Two: Control + Bev (%)	Arm Three: Control + Carbo (%)	Arm Four: Control + Bev and Carbo (%)
Leukopenia	12	13	13	**25**
Neutropenia	22	27	**56**	**67**
Thrombocytopenia	4	3	**20**	**26**
Hemoglobin	0	2	4	5
Febrile neutropenia	7	9	12	**24**
Nausea	4	4	3	8
Vomiting	2	2	2	4
Mucositis	2	0	1	4
Diarrhea	0	3	2	3
Hypertension	2	**12**	0	**10***
ALT elevation	0	3	0	3
Hypokalemia	3	1	6	2
Peripheral neuropathy	2	6	7	4
Fatigue	10	12	10	**20**
Pain	3	6	3	**11**

NOTE. Bold font indicates significant difference in incidence compared with other treatment arms. Early surgical complications requiring intervention ± bevacizumab: 9% versus 5%; delayed surgical complications requiring intervention ± bevacizumab: 4% versus 1%.
Abbreviations: Bev, bevacizumab; Carbo, carboplatin.
*One treatment-related fatality.

DISCUSSION

In addition to the trial reported here, two randomized studies have reported significant increases in pCR rates with the addition of bevacizumab to NACT in HER2-negative breast cancer.[14,15] Both employed control regimens consisting of an anthracycline-based combination and docetaxel. However, only in GeparQuinto (fifth German Preoperative trial) did adding bevacizumab significantly raise the pCR rate in 663 patients with TNBC (43% *v* 33%; two-sided $P = .007$). In NSABP (National Surgical Adjuvant Breast and Bowel Project) B-40, a significantly higher pCR rate was reported in hormone receptor–positive patients, whereas in 320 patients with TNBC, the pCR increase was not statistically significant (52% *v* 47%; two-sided $P = .34$). In both studies, treatment with bevacizumab was associated with higher rates of febrile neutropenia, hypertension, mucositis, hand-foot syndrome, reduced left ventricular function, postoperative complications, and treatment modifications. The impact of higher pCR rates with bevacizumab on long-term outcomes (RFS and OS) remains to be seen. However, in two recently reported large randomized trials—BEATRICE (Bevacizumab Adjuvant Therapy in

Triple-Negative Breast Cancer; N = 2,591, all of whom had TNBC) and E5103 (N = 4,994, of whom 1,079 had TNBC)—the addition of bevacizumab to anthracycline- and/or taxane-based adjuvant chemotherapy failed to improve invasive disease-free survival in patients with TNBC.[16,17] Given these findings, there is scant interest in further investigation of this antiangiogenic agent in early-stage TNBC.

Three randomized trials have addressed the addition of carboplatin to NACT in TNBC, of which CALGB 40603 is the largest and the only one to use a control regimen of ddAC and wP.[,18,19] GEICAM (Grupo Español de Investigación del Cáncer de Mama) 2006-03, a much smaller trial (N = 94), reported a nonsignificant drop in pCR (30% *v* 35%) when carboplatin was added to docetaxel after an anthracycline-based combination.[18] In GeparSixto (sixth German Preoperative trial), 315 patients with TNBC received wP 80 mg/m^2, nonpegylated liposomal doxorubicin 20 mg/m^2 once per week, and bevacizumab 15 mg/kg every 3 weeks, with or without weekly carboplatin AUC 2, for 18 weeks.[19] This regimen was associated with high rates of grade ≥ 3 hematologic toxicities, especially in patients assigned to carboplatin, and early treatment discontinuation because of toxicity (control arm, 36%; carboplatin arm, 49%). Despite these limitations, pCR breast/axilla (ypT0/isN0) in controls was 43% and increased to 57% with carboplatin (two-sided $P = .015$).

No TNBC study has compared carboplatin doses and schedules (AUC 6 every 3 weeks *v* AUC 2 once per week) concurrently with single-agent wP, but given results in other malignancies, the once-per-week regimen would likely cause less severe hematologic toxicities and might be as effective. Although the greater frequency of skipped doses, dose modifications, and early treatment discontinuations with the addition of carboplatin to wP in CALGB 40603 and GeparSixto could raise concern as to whether this might affect the ability of the chemotherapy to eradicate occult metastatic disease, thus increasing the risk of distant recurrence, the consistent association of pCR with improved RFS and OS in TNBC makes this unlikely.

A major limitation of available data is the lack of long-term outcomes, and none of these studies, including CALGB 40603, was powered to demonstrate statistically significant differences in RFS or OS. The US Food and Drug Administration–sponsored meta-analysis of randomized NACT trials confirmed that patients with TNBC who achieve a pCR have superior event-free survival (hazard ratio, 0.24; 95% CI, 0.18 to 0.33) and OS (hazard ratio, 0.16; 95% CI, 0.11 to 0.25) compared with those who do not.[2] However, even in TNBC, demonstrating that a 13% to 14% absolute increase in pCR rates (as seen with addition of carboplatin) leads to significant improvements in long-term outcomes would require a study many times larger than our trial,[20] because some patients will relapse despite achieving a pCR, whereas many who do not will remain free of disease. Despite this uncertainty, the US Food and Drug Administration has affirmed its commitment to considering applications for accelerated approval for new agents and indications supported by raising pCR rates in aggressive breast cancer subtypes like TNBC,[21,22] and in 2013, it granted accelerated approval to neoadjuvant pertuzumab in HER2-positive cancers on that basis.

TNBC is not a uniform entity.[23] By gene expression analysis, 70% to 80% of TNBCs display a basal-like profile, whereas the rest are a mix of other subtypes.[24] Other subclassifications have been suggested[25] and are undergoing clinical validation. *BRCA1*-mutation carriers account for 10% to 20% of TNBCs, and although *BRCA* mutations are uncommon in sporadic TNBC, dysfunctional *BRCA* pathways may also confer platinum sensitivity.[26] The availability of pretreatment tumor samples from patients enrolled onto CALGB 40603, together with treatment outcome data, provides a resource for identifying markers of response and resistance, including the effects of intrinsic subtype and other proposed classifications and a variety of candidate biomarkers. Ongoing analyses may lead to the identification of clinically relevant subsets to guide the design of future TNBC trials, including those studying the role of platinum analogs, alone or in combination with targeted agents such as poly (ADP-ribose) polymerase inhibitors.

In summary, higher pCR rates without demonstrated long-term benefits do not justify the routine addition of bevacizumab in stage II to III TNBC, especially given associated risks and costs. The addition of carboplatin to standard NACT for TNBC significantly improves pCR rates and may increase the percentage of patients eligible for BCS, but we await evidence that this translates into long-term benefits before recommending its routine use in clinical practice. Important objectives include identifying clinically relevant patient subsets, determining whether carboplatin should be added to existing regimens or substituted for other agents, and defining its optimal dose and schedule with regard to efficacy and toxicity. Results from CALGB 40603 and other studies justify consideration of definitive trials to determine whether inclusion of carboplatin leads to improvements in long-term outcomes in early-stage TNBC, preferably limited to biologically defined patient subsets believed most likely to benefit from this treatment.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Support

Supported in part by National Cancer Institute Grants No. CA31946 to the Alliance for Clinical Trials in Oncology, CA33601 to the Alliance Statistics and Data Center, CA076001 to the American College of Surgeons Oncology Group, CA025224 to the North Central Cancer Treatment Group, and CA32102 and CA46368 to the Southwest Oncology Group; by Genentech, a division of F. Hoffman-La Roche; by the Breast Cancer Research Foundation; and by funding provided by the American Recovery and Reinvestment Act to the Coalition for Cancer Cooperative Groups.

GLOSSARY TERMS

antiangiogenic: a process that involves blocking the generation of new blood vessels in a tumor, which disrupts the blood supply and thereby prevents tumor growth.

area under the curve (AUC): a measure of the amount of drug in the blood over a set period of time (eg, 24 hours) that can be used to determine drug exposure.

bevacizumab: also called Avastin (Genentech, South San Francisco, CA). Bevacizumab is a recombinant, humanized, monoclonal antibody that binds and neutralizes the vascular endothelial growth factor, thus acting as an antiangiogenic agent.

neoadjuvant therapy: the administration of chemotherapy prior to surgery. Induction chemotherapy is generally designed to decrease the size of the tumor prior to resection and to increase the rate of complete (R0) resections.

pathologic complete response: the absence of any residual tumor cells in a histologic evaluation of a tumor specimen.

residual cancer burden (RCB): an index to estimate the extent of residual invasive cancer in the breast and regional lymph nodes after neoadjuvant chemotherapy. RCB combines parameters derived from the review of routine pathology materials: two-dimensional extent of residual primary tumor, proportion of this primary tumor area that contains cancer cells, proportion of the residual primary cancer that is in situ, the number of involved regional lymph nodes, and the diameter of the largest nodal metastasis.

sentinel lymph node: the lymph node that is anatomically located such that it is the first site of lymph drainage from the location of the primary tumor. It is suspected and assumed that if a malignancy is going to disseminate via the lymphatic system, metastases will first be evident in the sentinel lymph node. In this manner, this lymph node is said to stand guard or sentinel over the metastatic state of the tumor. For many cancers, the sentinel lymph node is biopsied as part of the staging process and presence of macro- or micrometastases in the sentinel lymph node is a negative prognostic factor.

triple-negative phenotype: breast tumors that are negative for progesterone and estrogen and that underexpress HER2.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer: CALGB 40603 (Alliance)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Patents, Royalties, Other Intellectual Property: PAM50 and Hypoxia gene signatures

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Acknowledgment

Presented in part at the 36th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 10-14, 2013.

Appendix

The following institutions participated in this study: Bay Area Tumor Institute Community Clinical Oncology Program (CCOP), Oakland, CA; Jon M Grief, MD, Cancer Centers of the Carolinas, Greenville, SC; Jeffrey K. Giguere, MD (supported by National Cancer Institute [NCI] Grant No. CA29165), Christiana Care Health Services CCOP, Wilmington, DE; Stephen Grubbs, MD (supported by NCI Grant No. CA45418), Dana-Farber Cancer Institute, Boston, MA; Harold J. Burstein, MD, PhD (supported by NCI Grant No. CA32291), Dartmouth Medical School-Norris Cotton Cancer Center, Lebanon, NH; Konstantin Dragnev, MD (supported by NCI Grant No. CA04326), Duke University Medical Center, Durham, NC; Jeffrey Crawford, MD (supported by NCI Grant No. CA47577), Heartland Cancer Research CCOP, St Louis, MO; Alan P. Lyss, MD (supported by NCI Grant No. CA114558), Hematology-Oncology Associates of Central New York CCOP, Syracuse, NY; Jeffrey Kirshner, MD (supported by NCI Grant No. CA45389), Kansas City CCOP, Kansas City, MO; Rakesh Gaur, MD, Massachusetts General Hospital, Boston, MA; Jeffrey W. Clark, MD (supported by NCI Grant No. CA32291), Memorial Sloan Kettering Cancer Center, New York, NY; Clifford A. Hudis, MD (supported by NCI Grant No. CA77651), Mount Sinai Medical Center, Miami, FL; Michael A. Schwartz, MD (supported by NCI Grant No. CA45564), Mount Sinai School of Medicine, New York, NY; Lewis R. Silverman, MD (supported by NCI Grant No. CA04457), New Hampshire Oncology-Hematology, Concord, NH; Douglas J. Weckstein, MD, Northern Indiana Cancer Research Consortium CCOP, South Bend, IN; Rafat Ansari, MD (supported by NCI Grant No. CA86726), The Ohio State University Medical Center, Columbus, OH; Clara D. Bloomfield, MD (supported by NCI Grant No. CA77658), Rhode Island Hospital, Providence, RI; William Sikov, MD (supported by NCI Grant No. CA08025), Roswell Park Cancer Institute, Buffalo, NY; Ellis Levine, MD (supported by NCI Grant No. CA59518), Southeast Cancer Control Consortium CCOP, Goldsboro, NC; James N. Atkins, MD (supported by NCI Grant No. CA45808), State University of New York Upstate Medical University, Syracuse, NY; Stephen L. Graziano, MD (supported by NCI Grant No. CA21060), University of Chicago, Chicago, IL; Hedy L. Kindler, MD (supported by NCI Grant No. CA41287), University of Iowa, Iowa City, IA; Daniel A. Vaena, MD (supported by NCI Grant No. CA47642), University of Maryland Greenebaum Cancer Center, Baltimore, MD; Martin Edelman, MD (supported by NCI Grant No. CA31983), University of Missouri/Ellis Fischel Cancer Center, Columbia, MO; Karl E. Freter, MD (supported by NCI Grant No. CA12046), University of Oklahoma, Oklahoma City, OK; Shubham Pant, MD (supported by NCI Grant No. CA37447), Walter Reed Army Medical Center, Washington, DC; David C. Van Echo, MD (supported by NCI Grant No. CA26806), and Washington University School of Medicine, St Louis, MO; Nancy Bartlett, MD (supported by NCI Grant No. CA77440).

Table A1. No. of Patients With Serious AEs

AE	Arm One: Control	Arm Two: Control + Bev	Arm Three: Control + Carbo	Arm Four: Control + Bev and Carbo
Total	15	**39**	29	**46**
Febrile neutropenia	5	15	10	17
Infection without neutropenia	4	10	2	9
Nausea/vomiting/dehydration	1	5	5	6
Bleeding	0	2	0	5
Thromboembolic events	1	6	1	4
GI perforation	0	1	0	1

NOTE. Bold font indicates significant difference in incidence compared with other treatment arms.
Abbreviations: AE, adverse event; Bev, bevacizumab; Carbo, carboplatin.